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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/763,259	01/26/2004	Xiao-Chun (Chris) Le	033110-004	6473

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EXAMINER
WESSENDORF, TERESA D

ART UNIT	PAPER NUMBER
1639	

NOTIFICATION DATE	DELIVERY MODE
10/06/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com

Office Action Summary	Application No.	Applicant(s)	
	10/763,259	LE, XIAO-CHUN (CHRIS)	
	Examiner	Art Unit	
	TERESA WESSENDORF	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4,11,12,16 and 24-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4, 11-12, 16 and 24-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/17/09 has been entered.

Status of Claims

Claims 2-4, 11-12, 16 and 24-26 are pending and under examination.

Withdrawn Rejections

In view of the amendments to the claims, the 35 USC 112, 2nd paragraph rejection has been withdrawn.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: "**chemical** compound library". The

specification does not positively recite for a "chemical" compound library.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 24, as amended, is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The newly added claim limitation "fluorescence intensity of laser-induced fluorescence of the sample as a function of the relative" is not supported in the as-filed specification.

Applicant states that support can be found at pages 11 and 17 of the as-filed specification.

In reply, a review of these sections do not provide for support for the aforementioned new claim limitation. Page 11, for example, provides support for the newly added claim

limitation for the molecular weight of the probe being less than 20kDA.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 2-4, 11-12, 16 and 24-26, as amended and newly added, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record as reiterated below.

1. Claim 24 is unclear as to the measurement of the fluorescence intensity of laser-induced fluorescence of the sample as a function of the relative electrophoretic mobility of the binding complex and unbound probe is unclear and indefinite. This is unclear since the preceding step recites separation of the complex and unbound probe from the sample. It is further unclear whether the sample containing the binding factor is the one being measured i.e. determined by the method.

The entire step is confusing with the new amendments and appear to have no nexus among the claim steps i.e., steps b) and c). Cf. with the method steps in the specification at e.g., page 6, lines 10-15.

2. The term "specifically" in claim 24, steps (a) is a relative term which renders the claim indefinite given no characterizing or distinguishing features between the probe and binding factor. The term "specifically" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

It is not clear how specific binding can occur between two indistinguishable compounds as the probe and binding factor. It would appear that all samples will contain a binding factor for any type of probe. Thus, it is not clear as to the basis of "specific" binding.

Claim Rejections - 35 USC § 103

Claims 2-4, 11-12, 16 and 24-26, as amended and newly added, are rejected under 35 U.S.C. 103(a) as being unpatentable over Laing (6,331,392) in view of Le et al (6,132,968) for reasons of record and repeated below.

Laing discloses (throughout the Patent disclosure) at e.g., the abstract, a method for screening for bioactive compounds in particular those that bind to RNA sequences by assessing the stability and/or the conformation of an RNA target in the

presence and absence of test ligands (complex formation, as claimed), and identifying as a ligand any test ligand that causes a measurable change in target RNA stability and/or conformation. The effect of a ligand on target RNA stability and/or conformation is assessed by measuring the fluorescence polarization of a fluorescently labeled probe. Probes include molecules, which comprise fluorescent moieties whose measurable fluorescence properties, particularly polarization are sensitive to the stability and/or conformation of the target RNA as reflected in the binding state of the probe. Probe is any molecule to which a fluorescent moiety is attached, in which one or more fluorescence properties are sensitive to the stability and/or conformation of the target RNA and/or to the binding state of the probe. Suitable probe compounds include without limitation nucleic acids, particularly oligonucleotides; small RNA-binding molecules exemplified by 2-deoxystreptamine antibiotics, which bind the Rev-responsive element in HIV RNA, or other compounds that specifically recognize the major or minor groove of RNA; and proteins, and peptides derived therefrom, that recognize particular RNA sequences or conformations. See also Fig. 1. Test ligands may be derived from large libraries of synthetic or natural compounds. For example,

synthetic compound libraries are commercially available. See the specifics of the method in Example 1.

Laing further discloses at e.g., col.3, lines 15-21:

> Probes useful in practicing the invention include molecules which comprise fluorescent moieties whose measurable fluoresence properties, particularly polarization or anisotropy, are sensitive to the stability and/or conformation of the target RNA as reflected in the binding state of the probe.

Laing further discloses the stoichiometry i.e., ratios at e.g., col.8, line 1 up to col. 9, line 20:

> …determination of the absolute amounts or ratios of stabilized and non-stabilized or folded and unfolded target RNA may be carried out using probes which comprise one or more fluorescent moieties. Any stability-sensitive and/or conformation-sensitive probe to which an appropriate fluorescence moiety can be attached may be used in practicing the invention. For example, an oligonucleotide can be designed so that it will hybridize to a particular RNA target only when the RNA is in an unfolded conformation or to single-stranded regions in an otherwise folded conformation.

Laing does not disclose the use of capillary electrophoresis as recited in claim 2. However, Le discloses, throughout the Patent disclosure, electrokinetic chromatography by incorporating the teachings of Hjerten at e.g., col. 18, lines 45-57:

> The specificity of the methods provided herein is further enhanced by the use of capillary electrophoresis to separate fluorescent and non-fluorescent molecular entities. Capillary electrophoresis is described by Hjerten et al., U.S. Pat. No. 5,114,551, the entire contents of which are hereby incorporated by reference. Capillary electrophoresis includes the use of capillaries which are filled either with a gel (e.g., polyacrylamide) or with buffer. The use of capillary electrophoresis in the methods

> of the invention provides rapid sample analysis and permits the use of small sample volumes, making it particularly useful for analyzing samples of biological interest [See, e.g., Xian et al. (1996) Proc. Natl. Acad. Sci. USA 93:86-90].

Le further discloses at e.g., col.8, lines 30-50:

> Importantly, the methods of the invention are more accurate than prior art methods since they avoid potential artifacts which are caused by chemical or enzymatic nucleic digestion. Instead, the methods of the invention limit sample manipulation to extraction of nucleic acid sequences, incubation of the extracted nucleic acid sequences with proteins which are specific for the nucleic acid modification of interest and with nucleic acid sequence modification-specific molecules, and capillary electrophoresis.

Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use electrokinetic chromatography(EC) as capillary electrophoresis (CE) separation in the method of Laing as taught by Le above. Le teaches that said EC, particularly, CE is an accurate method that avoids potential artifacts caused by chemical or enzymatic nucleic digestion. One having ordinary skill in the art would have been motivated to use a capillary electrophoresis in the method of Laing for the advantages derived in said use as taught by Le above. One would reasonably expect that the use of said chromatography in the method of Laing would result in the separation of the bound from unbound complex since the technique of

chromatography has been known and employed in the art for such separation. Furthermore, it would have been obvious to determine the result effective variables such as the stoichemistry of a complex(compound) and /or binding affinity and correlate the results of one technique to the other. Such correlation would expectedly provide accurate quantitative or qualitative measurement of the complex being determined.

Response to Arguments

Applicant argues that neither the Laing '392 patent nor the Le '968 patent is prior art to the claimed subject matter of the present application, and thus may not properly form the basis of a prima facia case that the claims of the pending application are obvious under 35 U.S.C. § 103(a). The Laing '392 patent is not prior art to the present application because its December 18, 2001 issue date, which is its publication date, is not more than one year prior to the September 1,2000 priority date of the present application (35 U.S.C. § 102(b)). Nor was the Laing '392 patent a printed publication in this or another country before the invention date of the Applicant of the subject matter of the present application (35 U.S.C. § 102(a)) as indicated by at least the September 1, 2000 filing date of the application from which

the present application claims priority. Moreover, the Laing '392 patent has no effective (35 U.S.C. § 102(e)) as it was filed before November 29, 2000, the effective date of the present provisions of 102(e). At the time the '392 application was filed, its disclosure was kept in confidence by the USPTO pursuant to 35 U.S.C. § 122 and there is not indication that the application was published in another country. Thus, the disclosure of the Laing application was confidential (not known to others) under the applicable law prior to the issuance of the '968 patent. Like the Laing '392 patent, the publication date of the Le '968 patent is its issue date, October 17, 2000, which is not more than one year prior to either the September 1, 2000 or September 4, 2001 priority dates of the present application. Thus, the '968 patent is not prior art to the present application under any subsection of 35 U.S.C. § 102, and is therefore not prior art to the present application for purposes of obviousness under 35 U.S.C. § 103. Thus, the outstanding rejection of Claims 2-4, 11-12, 16, and 24 based on a combination of the teachings of the Laing '392 patent with the teachings of the Le '968 patent cannot establish a prima facia case of obviousness, as neither patent is prior art to the present application.

In reply, attention is drawn to MPEP 706.02(f)(1) to which the old law i.e., applications filed prior to the changes of Nov. 11, 2000 was in effect. Attention is drawn to Example 2:

> For reference publications and patents of patent applications filed under 35 U.S.C. 111(a), the prior art dates under 35 U.S.C. 102(e) accorded these references are the **earliest effective U.S. filing dates.** Thus, a publication and patent of a 35 U.S.C. 111(a) application, which claims *>benefit< under 35 U.S.C. 119(e) to a prior U.S. provisional application or claims the benefit under 35 U.S.C. 120 of a prior nonprovisional application, would be accorded the earlier filing date as its prior art date under 35 U.S.C. 102(e), assuming the earlier-filed application has proper support for the subject matter as required by 35 U.S.C. 119(e) or 120. Please see also the accompanying diagrams. (Emphasis added.)

Thus, the Laing reference is a proper prior art as the effective filing date of the Laing reference is March 5, 1997, which is prior to the instant effective filing date of 9/1/2000.

Double Patenting

Claims 2, 11, 16 and 24-26, as amended and newly added, are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 9 of U.S. Patent No. 6,132,968('968 Patent) in view of 6,331,392 ('392 Patent) for reasons reiterated below.

The claims and specification of the '968 Patent claims/discloses a method for quantitating at least one modification of interest in a nucleic acid sequence contained in a sample, comprising: a) providing: i) a sample suspected of containing a nucleic acid sequence comprising the at least one modification of interest; ii) a first polypeptide sequence capable of specifically binding to the at least one modification of interest, and iii) a fluorescently labeled second polypeptide sequence capable of specifically binding to the first polypeptide sequence; b) combining the sample, the first polypeptide sequence and the fluorescently labeled second polypeptide sequence to produce a fluorescently labeled second polypeptide sequence:first polypeptide sequence:nucleic acid sequence complex, (step b, as claimed) and a fluorescently labeled second polypeptide sequence:first polypeptide sequence complex; c) separating the fluorescently labeled second polypeptide sequence:first polypeptide sequence:nucleic acid sequence complex, the fluorescently labeled second polypeptide sequence:first polypeptide sequence complex and the fluorescently labeled second polypeptide sequence by capillary electrophoresis; d) detecting the separated fluorescently labeled second polypeptide sequence:first polypeptide sequence:nucleic acid sequence complex by laser-induced fluorescence; and e) quantitating the separated second polypeptide sequence:first polypeptide sequence:nucleic acid sequence complex, thereby quantitating the at least one modification of interest in the nucleic acid sequence. Example 1, col. 20 up to Example 6, col. 27 provides detail steps of the method and the specific probes and polypeptides used in the method. The '968 Patent does not disclose fluorescence polarization. However, the '392 patent discloses the alternativeness of fluorescence and fluorescence polarization. It further discloses that particularly polarization is sensitive to the stability and/or conformation of the target RNA as reflected in the binding state of the probe. Accordingly, one would have been motivated to use fluorescence polarization in the method of the '968 Patent for the benefits derived therein as taught by the '392 Patent.

Response to Arguments

In the prior response, Applicant asserted that the obviousness double patenting rejection as to the '392 patent was made in

error as there is no common assignee or inventor between the present application and the Laing '392 patent. To support this position, Applicant's representative intended to refer to MPEP 804, Definition of Double Patenting, in particular to Chart II-B Conflicting Claims between an Application and a Patent, at MPEP page 800-16 of the current MPEP. The chart indicates that where an application and a patent have no common assignee or inventor and do not have a proper joint research exclusion under section 103(c), the proper rejection to be made is under section 102(e)/103(a), not a non-statutory double patenting rejection. Here the Laing '392 patent has no common assignee or inventor and is not 102(e)/103(a) prior art, as the patent issued from an application that was filed on March 5, 1998. The Laing '392 patent does not have an effective date 102(e) as prior art. Because the Laing '392 patent does not have an effective 102(e)/103(a) date, it is not available as prior art against the present application. Likewise, the Le '968 patent is not prior art to the present application. Like the Laing '392 patent, the Le '968 patent was filed and issued prior to November 29, 2000. Its issue/publication date, October 17, 2000, is after the September 1, 2000 priority date of the present application.

In response, applicant is confusing the application of the prior art to the instant double patenting rejection. The ‘392 patent (Laing) is not used as a primary reference for the obviousness double patenting rejection (please see above), it is the ‘968 Patent (Le, Xiao-Chun). Le is an inventor common to the '968 Patent and (the sole inventor of) the present application. The ‘392 secondary reference, which when combined with the ‘968 primary (Le) reference renders the claim method prima facie obvious.

Thus, the combined teachings of the references, which disclose all the elements of the claim method renders the claim prima facie obvious.

{This rejection can be overcome by filing a terminal disclaimer.]

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA WESSENDORF whose telephone number is (571)272-0812. The examiner can normally be reached on flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TERESA WESSENDORF/
Primary Examiner, Art Unit 1639